NIH RELAIS Document Delivery

NIH-10061928

NIH -- W1 CA671K

MICHELLE MAHER
NCI/DCPC
6116 Executive Blvd. Suite 705 MSC8314
ROCKVILLE, MD 20892-8314
URUGUAY

ATTN:		SUBMITTED:	2001-11-06 14:09:01
PHONE:	301-496-0478	PRINTED:	2001-11-07 11:56:59
FAX:	301-435-8645	REQUEST NO.:	NIH-10061928
E-MAIL:		SENT VIA:	LOAN DOC 4917373

NIH Fiche to Paper Journal

TITLE:	CANCER
PUBLISHER/PLACE:	Wiley New York Ny
VOLUME/ISSUE/PAGES:	1988 Oct 1;62(7):1451-7 1451-7
DATE:	1988
AUTHOR OF ARTICLE:	Schatzkin A; Baranovsky A; Kessler LG;
TITLE OF ARTICLE:	Diet and cancer. Evidence from associations of mul
ISSN:	0008-543X
OTHER NOS/LETTERS:	Library reports holding volume or year 0374236 3416284
SOURCE:	PubMed
CALL NUMBER:	W1 CA671K
NOTES:	Please email all copy orders
REQUESTER INFO:	AC956
DELIVERY:	E-mail: mm130D@nih.gov
REPLY:	Mail:

Diet and Cancer

Evidence From Associations of Multiple Primary Cancers in the SEER Program

ARTHUR SCHATZKIN, MD, DrPH,* ANNE BARANOVSKY, MS,† AND LARRY G. KESSLER, ScD†

The occurrence of multiple primary cancers may reflect common etiologic factors. We investigated the extent to which the diet and cancer hypothesis was supported by data from the Surveillance, Epidemiology, and End Results (SEER) Program on multiple primary associations. Cancers of the colon/rectum and prostate in men, and those of the breast, colon/rectum, and uterine corpus in women, were hypothesized *a priori* to be diet-related cancers. Of the eight multiple primary associations among diet-related cancers that were possible in men and women, relative risks (RR) of a second diet-related primary cancer developing after a first diet-related primary ranged from 1.06 to 1.43. The lower bound of the 99% confidence intervals (CI) for five of these associations exceeded 1.00, and fell between 0.95 and 0.99 for the other three associations. The observed multiple primary associations were compatible with the existence of common etiologic dietary elements. However, hormonal, immunologic, and medical care factors shared by these malignancies must be considered as alternative explanations for these findings.

***Cancer* 62:1451–1457, 1988.**

IT IS well recognized that persons with a history of cancer at specific sites are at increased risk for a second primary cancer developing at certain other sites.[1–3] This is particularly true for tobacco-related cancers.[4] The elucidation of risk factors common to multiple primary cancers at specific sites is a valuable product of research in this area.

A relation between diet and cancer at a number of sites has been suggested by numerous laboratory, correlation, and analytic epidemiologic studies.[5–9] Other studies have shown ecologic correlations between rates of cancer of more than one site, including cancers of the breast and colon[10,11] or cancers of the prostate, colon, breast, and uterine corpus.[12] If particular dietary patterns were causally related to several types of cancer, we would expect to see associations of these allegedly diet-related cancers in an analysis of multiple primary cancers.

In this study, we explore the evidence for multiple primary associations of potentially diet-related cancers in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI).

From the *Cancer Prevention Studies Branch, Cancer Prevention Research Program, and the †Surveillance and Operations Research Branch, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland.

The authors thank Drs. D. Yvonne Jones, Elaine Lanza, and Gladys Block for assistance in the selection of hypothetical diet-related cancers; Drs. Benjamin F. Hankey, Edward J. Sondik, Philip R. Taylor, and Charles C. Brown for suggestions and critical comments; and Mr. Arnold Potosky for assistance with data manipulation.

Address for reprints: Arthur Schatzkin, MD, DrPH, National Institutes of Health, National Cancer Institute, Blair Building, Room 6A-01, 9000 Rockville Pike, Bethesda, MD 20892.

Accepted for publication March 2, 1988.

Materials and Methods

First Primary Cancers: The SEER Data

We have used data on primary invasive cancers reported by the nine standard population-based registries of the SEER Program.[13] These areas included Connecticut, Hawaii, Iowa, New Mexico, Utah, and the metropolitan areas of Detroit, Atlanta, Seattle, and San Francisco–Oakland. First primary cancers were diagnosed from 1973 through 1981, and follow-up continued through 1983. Only cases with follow-up information were included. The data set comprises cancers in men and women of all race and treatment groups, and cancers with and without microscopic confirmation. The total number of first primary cancers studied in this analysis was 176,021 among men and 181,064 among women, comprising 427,104 and 653,982 person-years at risk, respectively.

Definition of Multiple Primary Cancers

Two cancers, A and B, are said to be multiple primary cancers if each arises within the same person but neither represents a recurrence or metastasis from the other. (A metastatic lesion is often referred to as a "secondary" cancer.) A person can have more than two primary cancers, and multiple primary cancers can arise within the same anatomical site. A series of operational definitions

and rules based on anatomic site, diagnosis date, histologic type, tumor behavior, and laterality have been formulated by the SEER staff at the NCI for distinguishing independent primary cancers from cases of recurrence or metastasis.[14,15] Histologic type is frequently used to distinguish multiple primaries. A single lesion of more than one histologic type is a single primary site, coded to the highest cytology. However, multiple lesions of different histologic types within a single site or in different sites are separate primaries, whether simultaneous or not. A second lesion of the same histologic type in the same site as the first cancer (except bladder) is a separate primary if diagnosed after 2 months, unless stated as recurrent. For some sites, such as the colon and rectum, each subcategory is considered a separate primary (*i.e.*, cecum, transverse colon, or sigmoid colon).

Investigators of multiple primary cancers have generally excluded from analysis persons with cancer B as a second primary cancer relative to initial primary cancer A if B was found at the same time as or shortly after the time A was diagnosed. However, because the simultaneous occurrence of two or more cancers is consistent with the hypothesis of common risk factors, we have chosen to retain those multiple primary cancers. In instances of simultaneous diagnosis of two or more primaries, the index cancer site was based on the cancer with the worst prognosis, furthest extension, or most virulent histologic type. We did not include in the analysis cancer pairs with both cancers of the same site (*i.e.*, breast–breast).

Analytic Approach

The relative risk (RR) of a second primary cancer developing after a first primary cancer was estimated as the ratio of observed to expected cases over all available years of follow-up contained in the SEER registries. The expected number of cases was determined by applying SEER age–sex–time–site-specific incidence rates to person-years at risk, using a modification of Monson's program for person-years analysis.[16] The Monson program estimates expected cases by explicitly controlling for the age of the group under examination. Person-years at risk were based on length of observation from date of diagnosis of the first primary to date of diagnosis of a second primary of any site, date of death, date lost to follow-up, or December 31, 1983, whichever came first. Because the discovery of a second cancer during the same month as the first one would provide no additional person-years, a fact that might have inflated RR estimates, we used one half of 1 month as an estimate of person-years of observation for each such simultaneous "second" primary cancer. (The simultaneous cancers were a relatively small proportion of the total multiple primaries.) Byar's approximation to the Poisson distribution was used to calculate 95% and 99% two-sided confidence intervals (CI) about the RR.[17]

We also calculated the observed and expected number of cases for each year after the diagnosis of a first primary tumor, and graphed the cumulative excess risk (over time) of the second primary tumor. The final point on these curves corresponded to the RR described above.

A Priori *Designation of Diet-Related Cancers*

A list of potentially diet-related cancers was generated from findings of previous laboratory and/or epidemiologic studies,[5–7] in conjunction with suggestions made by researchers in nutrition and epidemiology at the NCI. For men, the cancer sites selected were the colon/rectum[5,6,18–21] and prostate.[5,6,9,22,23] For women, the sites were the breast,[5,6,24,25] colon/rectum,[5,6,18–21] and uterine corpus.[26–28] We hypothesized that if cancers A and B were related to common dietary components, then there would be an excess risk of cancer B for those in which cancer A initially developed. Conversely, that there would be an elevated risk of A in those first contracting B.

We readily acknowledge that the evidence in the diet and cancer area is complex and inconsistent. Some dietary constituents have been suggested to increase cancer risk (*i.e.*, dietary fat in cancers of the breast and colon), whereas other dietary factors have been proposed to protect against cancer (*i.e.*, dietary fiber in colon cancer), and it is likely that complex dietary interactions would be involved in carcinogenesis. However, although etiologic dietary factors for several cancers may differ, it is possible that some of these dietary factors will be present together in certain aggregate diets. For example, diets with relatively high levels of saturated fat are generally diets with relatively low levels of dietary fiber and possibly vegetable-based micronutrients. Therefore, if cancer A were positively associated with dietary fat and cancer B were inversely related to dietary fiber, we would expect to see a multiple primary association between A and B.

The Multiple Comparisons Problem

Because a potentially large number of multiple primary pairs were to be explored, we were concerned with statistical protection against spuriously significant findings. In the case of many tests of similar statistical hypotheses within the same data set, one would expect some associations significant at the conventional 5% level to be random rather than true associations.[29] A frequent approach taken to address this problem is the use of the Bonferroni CI. This approach provides the investigator with a chosen level of Type I (or alpha) error for the entire family of tests by reducing the rejection region against which each of the individual null hypotheses is tested.[30] The statistical

TABLE 1. Study Population by Site of Index Case and Sex

ICD–O codes	First primary cancer site	Men		Women	
		Persons at risk	Person-years	Persons at risk	Person-years
153, 154	Colon/rectum	40,916	113,789	42,882	126,103
174	Female breast	—	—	79,553	340,167
179, 182	Uterine corpus	—	—	26,170	126,720
185	Prostate gland	50,417	174,897	—	—
162	Trachea, bronchus, lung	59,121	67,364	22,803	32,964
140–149, 150, 160, 161, 163, 164.1–165	Other smoking-related sites	25,567	71,054	9656	28,028

ICD–O: International Classification of Diseases for Oncology (Geneva: World Health Organization, 1976).

hypothesis that most reflected the underlying premise of this study was that the RR estimates for all diet-related multiple primary pairs were significant. In contrast, the conventional Bonferroni correction is used in an exploratory analysis to correct for the occurrence of a spurious significant result, when the hypotheses are grouped within hypothesis "families." Rather than provide an explicit correction, we studied the RR of second primaries using both the conventional 95% CI (for each test) and a more conservative 99% CI estimate. Because we have grouped the significance tests into families defined by presumed dietary agents within sex-specific cancer sites (*i.e.*, colon/rectum–prostate in men), the more stringent 99% limits represent slightly more conservative family-wise alpha levels than would have been used under the conventional Bonferroni adjustment procedure.

"Control" Analysis: Examination of Nonspecific Explanations

Although common etiologic factors are a plausible explanation for statistically significant multiple primary cancer associations, alternative explanations can be invoked. These include generalized cancer susceptibility, heightened medical surveillance of persons with an initial primary, and effects of treatment of the first primary. To rule out these "nonspecific" explanations, we conducted a control analysis based on several cancers for which cigarette smoke is a well-established etiologic agent. We studied multiple primary associations between our putative diet-related cancers and both lung cancer and an aggregate category of smoking-related cancers that included cancers of the buccal cavity and pharynx, esophagus, and respiratory sites other than the lung. If generalized susceptibility, heightened surveillance, and/or treatment effects were responsible for multiple primary associations among our diet-related cancers, then we would expect to see direct associations between diet-related and smoking-related cancers. Thus, our statistical hypothesis here was that all associations were null. We also plotted the cumulative excess RR (over time) for the diet-related and smoking-related cancer pairs to provide comparisons with the survival results from pairs of the purported diet-related cancers.

Data are presented separately for men and women in Table 1 on the number of persons and person-years at risk for each of the first primary cancer sites selected.

Results

Figure 1 shows RR for diet-related cancers. The first primary is listed first in all hyphenated pairs. In men, for example, colon/rectum–prostate indicates that the first primary is colorectal cancer and the second primary is prostate cancer. The wider upper bars and narrower lower bars represent the 99% and 95% CI, respectively. In general, the differences between the two interval estimates were not large. An elevated RR was evident among men for colon/rectum–prostate (RR, 1.41). For prostate–colon/rectum, the RR was 1.1 with a 99% CI (range 0.96 to 1.17). (In the text below, only the 99% CI are presented.)

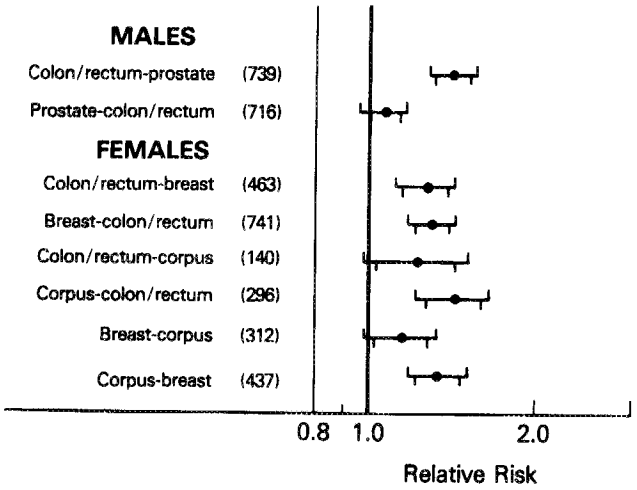

FIG. 1. RR and CI (99% and 95%) for diet-related cancer pairs. The number of cases is in parentheses.

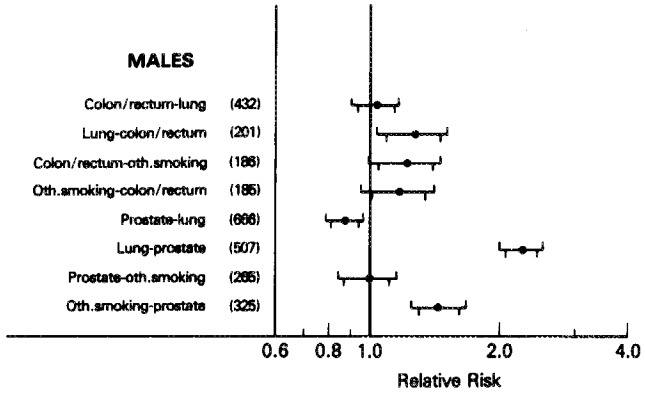

FIG. 2. RR and CI (99% and 95%) for diet/smoking associations. The number of male cases is in parentheses.

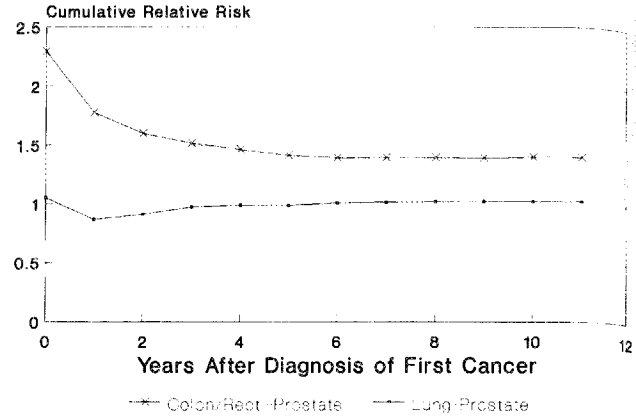

FIG. 4. Cumulative RR over time since diagnosis of first primary cancer for colon/rectum–prostate and colon/rectum–lung cancer in men.

The female sites chosen (breast, colon/rectum, and uterine corpus) provided six potential pairs for analysis. RR for four of the pairs were as follows (Fig. 1): colon/rectum–breast (RR, 1.27), breast–colon/rectum (RR, 1.30), corpus–colon/rectum (RR, 1.43), and corpus–breast (RR, 1.33). Ninety-nine percent CI for each of these pairs excluded 1.0. RR for the remaining two pairs reached borderline significance (colon/rectum–corpus [RR, 1.22; range, 0.97 to 1.51] and breast–corpus [RR, 1.14; range, 0.98 to 1.32]).

Figures 2 and 3 depict for men and women, respectively, the RR for various pairs consisting of a diet-related and a smoking-related cancer. Among men, there were eight potential pairs (two diet-related cancers considered reciprocally with two smoking-related cancers). RR were 2.25 and 1.44, respectively, for lung–prostate and other smoking-related-prostate. Ninety-nine percent CI for these two pairs excluded 1.0. Smaller elevations in RR were seen for the following three additional pairs among men: lung–colon/rectum (RR, 1.26; range, 1.04 to 1.50), colon/rectum–other smoking-related (RR, 1.21; range, 0.99 to 1.45), and other smoking-related–colon/rectum (RR, 1.16; range, 0.95 to 1.40). The remaining three diet-smoking pairs showed minimal or no association.

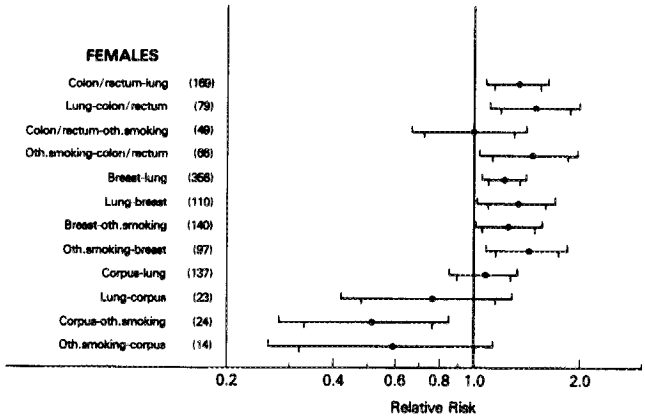

FIG. 3. RR and CI (99% and 95%) for diet/smoking associations. The number of female cases is in parentheses.

For women, there were 12 potential diet-related/smoking-related pairs. Increased RR, with the CI excluding 1.0, were seen for the following four pairs: colon/rectum–lung (RR, 1.21), and other smoking-related-breast (RR, 1.42). RR were elevated for the following three pairs, but the lower boundary of the CI was at or very near 1.0: other smoking-related–colon/rectum (RR, 1.45; range, 1.03 to 1.97), lung–breast (RR, 1.32; range, 1.02 to 1.68), and breast–other smoking-related (RR, 1.25; range, 1.00 to 1.55). Negligible associations were evident for the other five pairs.

Because both dietary factors and smoking have been suggested to play a role in the etiology of cancer of the pancreas,[31-34] we studied pancreatic cancer separately from the other potentially diet-related and smoking-related cancers. Because the survival time for cancer of the pancreas as a first cancer is extremely short (5-year relative survival rate [2.7%]),[35] the reduction in risk-time for the development of a possible second cancer would have been too great for generation of meaningful results. Therefore, we looked at pancreatic cancer only as a subsequent site in relation to the hypothesized diet-related and smoking-related cancers. RR were slightly elevated in both men and women for pancreatic cancer after diet-related cancers, but only associations for prostate–pancreas cancers in men (RR, 1.17; range, 0.94 to 1.45) and corpus–pancreas cancers in women (RR, 1.35; range, 0.91 to 1.92) attained even marginal significance. The risk elevations for pancreatic cancer after smoking-related cancers were

generally higher than those for pancreatic cancer after diet-related cancers. The RR estimate for lung–pancreas cancer in men was 1.58 (range, 1.06 to 2.25) and in women 2.86 (range, 1.65 to 4.60).

The results of the survival analyses indicated that the risk of a second primary tumor was greatest at the time of or shortly after diagnosis of the first primary. Figures 4 and 5 illustrate this. In Figure 4, we see that the RR for (second primary) prostate cancer at or within the first year of diagnosis of (first primary) colorectal cancer was approximately 2 and dropped to approximately 1.4 by the end of the follow-up period. We also see here that the colon/rectum–prostate RR remained considerably greater than the colon/rectum–lung RR (over time). In Figure 5, we again see a drop in the RR for (second primary) colorectal cancer shortly after diagnosis of (first primary) uterine corpus cancer. The corpus–colon/rectum RR also remained larger than the corpus–lung RR for the duration of the follow-up period.

Results from survival analyses of the other diet-related/diet-related and diet-related/smoking-related pairs did not differ qualitatively from the RR estimates presented in Figures 1, 2, and 3 (which represent the final data point on the survival curves, as in Figures 4 and 5, for each of the multiple primary pairs).

Discussion

Because data on specific exposures are lacking in this and similar studies of multiple primary cancer associations, support for a given etiologic hypothesis is necessarily indirect. The clustering of multiple primary associations among cancers of the lung, mouth, esophagus, pancreas, bladder, kidney, and, for women, cervix, supports a common etiology for these tumors. Several decades of epidemiologic and laboratory studies show that cigarette smoking is a common causal factor for these cancers, and smoking becomes the most likely explanation for the observed multiple primary associations.[36]

The picture that has emerged from previous investigations of diet and cancer is less clear than that emerging from the smoking and cancer studies. This is due, in part, to the fact that the diet is complex and difficult to measure accurately. Our goal in this study was simply to determine if the multiple primary cancer data were compatible with a common dietary etiology for certain cancers in men and women. We concluded that the observed multiple primary associations for those cancers specified *a priori* as potentially diet-related were generally consistent with the notion of common dietary risk factors. Both of the associations among men and all six of the associations among women were significant or marginally significant at the 99% CI.

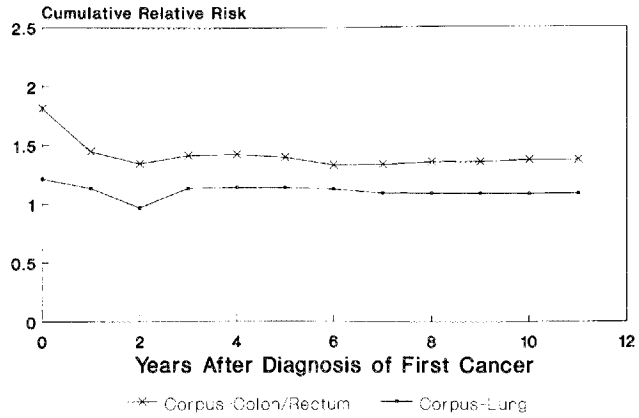

FIG. 5. Cumulative RR over time since diagnosis of first primary cancer for corpus–colon/rectum and corpus–lung cancers in women.

We note, however, that the magnitudes of the RR in these associations were not large, unlike the smoking-related associations.

Although these data do support the common dietary factor hypothesis, it is clearly possible that other common exposures underlie the observed multiple primary associations. There may be common hormonal processes at work here. Endocrine factors are likely to play a role in cancers of the breast and uterine corpus in women.[37–42] Laboratory investigations of colonic carcinogenesis have suggested a role for sex hormones,[43] and epidemiologic associations between colon cancer and various reproductive risk factors in women have been reported.[44] Hormonal factors in men have been implicated in prostate carcinogenesis.[37] We note, however, that diet may mediate endocrine processes in complex ways, and recent evidence suggests that the hormonal milieu is indeed influenced by the intake of certain dietary constituents.[45–51]

Our control analysis of multiple primary associations between our predesignated diet-related cancers and cancers known to be smoking-related was intended to explore the specificity of the diet-related associations. The absence of multiple primary associations between the diet-related and smoking-related cancers would have argued against such nonspecific explanations as increased cancer susceptibility or heightened tumor surveillance (after a first primary cancer), or consequences of treatment of the first primary malignancy. However, five of eight potential diet/smoking pairs in men and eight of 16 pairs in women were significant or marginally significant. Although the diet/smoking multiple primary associations were not as consistent here as they have been reported to be among strictly smoking-related cancers[4] or as they were among our putative diet-related cancers, we cannot conclude that the diet/smoking associations all were null.

A role for heightened medical surveillance would certainly seem to be supported by the fact, demonstrated in the survival analyses, that the excess risk of a second primary diet-related tumor was greatest at or shortly after the time of diagnosis of a first primary diet-related malignancy. Moreover, the lack of excess risk (and, in fact, a nonsignificant reduced risk) of second primary corpus cancer after first primary lung or other smoking-related cancer could be explained on the basis of an antiestrogenic effect of smoking[52] rather than the absence of, for example, heightened medical surveillance. Thus, on the basis of the diet/smoking associations, we cannot rule out such nonspecific explanations as increased cancer susceptibility, medical vigilance, and/or treatment effects after a primary cancer.

We should note, however, that the diet/smoking results are not incompatible with the concept of common dietary etiology, in that cigarette smoking is associated with certain dietary patterns. Smoking has been shown, in a number of studies, to be directly related to dietary intake of saturated fat, in both grams per day and as a percentage of total energy.[53] Therefore, if dietary fat were related to colon cancer, one might see a multiple primary association between colon/rectum and lung cancers.

In summary, this study demonstrates multiple primary associations among cancers hypothesized to be diet-related. Although alternative phenomena (*i.e.*, intensified medical surveillance) may account for part or even all of these findings, these associations may reflect common dietary risk factors operating independently or in conjunction with endocrine processes or other exposures.

REFERENCES

1. Schoenberg BS. Multiple primary malignant neoplasms. The Connecticut experience, 1935–1964. *Recent Results Cancer Res* 1977; 58: 1–173.
2. Schottenfeld D. Multiple primary cancers. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. Philadelphia: WB Saunders, 1982; 1025–1035.
3. Boice JD, Storm HH, Curtis RE *et al.* eds. Multiple primary cancers in Connecticut and Denmark. *NCI Monogr* 1985; 68:1–437.
4. Wynder EL, Mushinski MH, Spivak JC. Tobacco and alcohol consumption in relation to the development of multiple primary cancers. *Cancer* 1977; 40:1872–1878.
5. National Research Council. Diet, Nutrition, and Cancer. Washington, DC: National Academy Press, 1982; 1–478.
6. Reddy BS, Cohen LA. Diet, Nutrition, and Cancer: A Critical Evaluation. Boca Raton, FL: CRC Press, 1986; Vol. 1 and Vol. 2.
7. Armstrong BK, McMichael AJ, MacLennan R. Diet. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. Philadelphia: WB Saunders, 1982; 419–433.
8. Ip C, Birt DF, Rogers AE, Mettlin C, eds. Dietary fat and cancer. In: Progress in Clinical and Biologic Research, vol. 222. New York: Alan R Liss, 1986.
9. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975; 15:617–631.
10. Howell MA. The association between colorectal cancer and breast cancer. *J Chronic Dis* 1976; 29:243–261.
11. Jansson B, Seibert B, Speer JF. Gastrointestinal cancer: Its geographic distribution and correlation to breast cancer. *Cancer* 1975; 36: 2373–2384.
12. Berg JW. Can nutrition explain the pattern of international epidemiology of hormone-dependent cancers. *Cancer Res* 1975; 35:3345–3350.
13. Horm JW, Asire AJ, Young JL, Pollack, eds. SEER Program: Cancer Incidence and Mortality in the United States 1973–81. Bethesda, MD: National Institutes of Health, 1984; NIH publication no. 85–1837.
14. Demographic analysis. In: Code Manual: The SEER Program. Bethesda, MD: National Institutes of Health, revised 1979; NIH publication no. 79-1999.
15. Demographic analysis. Code Manual: The SEER Program. Bethesda, MD: National Institutes of Health, revised 1984.
16. Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomet Res* 1974; 7:325–332.
17. Rothman KJ, Boice JD. Epidemiologic Analysis With a Programmable Calculator. Washington, DC: US Government Printing Office, 1979; NIH publication no. 79-1649.
18. Howell MA. Diet as an etiological factor in the development of cancers of the colon and rectum. *J Chronic Dis* 1975; 28:67–80.
19. Zaridze DG. Environmental etiology of large-bowel cancer. *J Natl Cancer Inst* 1983; 70:389–400.
20. Ziegler RG, Devesa SS, Fraumeni JF. Epidemiologic patterns of colorectal cancer. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important Advances in Oncology. Philadelphia: JB Lippincott, 1980; 209–232.
21. Lanza E, Greenwald P, Eddy GA. Dietary fiber in the reduction of colon cancer risk. *J Am Dent Assoc* 1987; 87:1178–1188.
22. Blair A, Fraumeni JF. Geographic patterns of prostate cancer in the United States. *J Natl Cancer Inst* 1978; 61:1379–1384.
23. Snowden DA, Phillips RL, Choi W. Diet, obesity, and risk of fatal prostate cancer. *Am J Epidemiol* 1984; 73:341–352.
24. Gray GE, Pike MC, Henderson BE. Breast cancer incidence and mortality rates in different countries in relation to known risk factors and dietary practices. *Br J Cancer* 1976; 39:1–7.
25. Carroll KK, Khor HT. Dietary fat in relation to tumorigenesis. *Prog Biochem Pharmacol* 1975; 10:308–353.
26. Kelsey JL, Hildreth NG. Cancer of the corpus uteri. In: Kelsey JL, Hildreth NG, eds. Breast and Gynecologic Cancer Epidemiology. Boca Raton, FL: CRC Press, 1983; 71–91.
27. Gusberg SB. The changing nature of endometrial cancer. *N Engl J Med* 1980; 302:729–730.
28. Armstrong BK. Diet and hormones in the epidemiology of breast and endometrial cancer. *Nutr Cancer* 1979; 1:90–95.
29. Alt FB. Bonferroni inequalities and intervals. In: Katz S, Johnson NL, eds. Encyclopedia of Statistical Sciences. New York: John Wiley & Sons, 1982; 294–300.
30. Grove WM, Andreason NC. Simultaneous tests of many hypotheses in exploratory research. *J Nerv Ment Dis* 1982; 170:3–8.
31. Wynder EL, Mabuchi K, Maruchi N, Fortner JG. Epidemiology of cancer of the pancreas. *J Natl Cancer Inst* 1973; 50:645–667.
32. Gordis L. Epidemiology of pancreatic cancer. In: Lilienfeld AM, ed. Reviews in Cancer Epidemiology. New York: Elsevier, 1980; 84–117.
33. Mack TM. Pancreas. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. Philadelphia: WB Saunders, 1982; 638–667.
34. Longnecker DS, Wiebkin P, Schaeffer BK, Roebuck BD. Experimental carcinogenesis in the pancreas. *Int Rev Exp Pathol* 1984; 26: 177–229.
35. Young JL, Ries LG, Pollack ES. Cancer patient survival among ethnic groups in the United States. *J Natl Cancer Inst* 1984; 73:341–352.
36. United States Office on Smoking and Health. Smoking and Health:

Report of the Surgeon General. 1979. DHEW publication no. (PHS) 79-50066; Washington, DC: Government Printing Office.

37. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. *Cancer Res* 1982; 42: 3232–3239.

38. MacMahon B, Cole P, Brown J. Etiology of human breast cancer: A review. *J Natl Cancer Inst* 1973; 50:21–42.

39. Kelsey JL. A review of the epidemiology of human breast cancer. *Epidemiol Rev* 1979; 1:74–109.

40. Thomas DB. Factors that promote the development of human breast cancer. *Environ Health Perspect* 1983; 50:209–218.

41. Gambrell RD, Bagnell CA, Greenblatt RB. Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: Review. *Am J Obstet Gynecol* 1983; 146:696–707.

42. Greenblatt RB, Gambarell RD, Stoddard LD. The protective role of progesterone in the prevention of endometrial cancer. *Pathol Res Pract* 1982; 174:297–318.

43. Pozharisski KM, Likhachev AJ, Klimashevski VF, Shaposhnikov JD. Experimental intestinal cancer research with special reference to human pathology. *Adv Cancer Res* 1979; 30:165–237.

44. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: A review and hypothesis. *J Natl Cancer Inst* 1980; 65:1201–1207.

45. Chan PC, Didato F, Cohen LA. High dietary fat elevation of rat serum prolactin and mammary cancer. *Proc Soc Exp Biol Med* 1973; 149:133–135.

46. Chan PC, Head JF, Cohen LA, Wynder EL. Influence of dietary fat on the induction of rat mammary tumors by N-nitrosomethylurea: Associated hormone changes and differences between Sprague–Dawley and F344 rats. *J Natl Cancer Inst* 1977; 59:1279–1283.

47. Hill P, Wynder EL. Diet and prolactin release. *Lancet* 1976; 2: 806–807.

48. Hill P, Chan P, Cohen L, Wynder EL, Kuno K. Diet and endocrine-related cancer. *Cancer* 1977; 39:1820–1826.

49. Schultz TD, Leklem JE. Nutrient intake and hormonal status of premenopausal vegetarian Seventh-day Adventists and premenopausal nonvegetarians. *Nutr Cancer* 1983; 4:247–259.

50. Goldin BR, Adlercreutz H, Gorbach SL *et al.* Estrogen excretion patterns and plasma levels in vegetarian and omniverous women. *N Engl J Med* 1982; 307:1542–1547.

51. Goldin BR, Adlercreutz H, Gorbach SL *et al.* The relationship between estrogen levels and diets of Caucasian American and Oriental immigrant women. *Am J Clin Nutr* 1986; 44:945–953.

52. Lesko SM, Rosenberg L, Kaufman DW *et al.* Cigarette smoking and the risk of endometrial cancer. *N Engl J Med* 1985; 313:593–596.

53. Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Licitra LM. Serum cholesterol and cancer in the NHANES I Epidemiologic Followup Study. *Lancet* 1987; 2:298–301.